Ichthyosiform syndromes (Syndromic ichthyoses)

(1) Netherton's syndrome (ichthyosis linearis circumflexa)

- AR
- Mutations in the **serine protease inhibitor Kazal type 5 gene (SPINK5)**
- ***Triad***
  - **ichthyosis linearis circumflexa**
  - **atopy**
  - **Trichorrhexis invaginata**

(2) Sjögren–Larsson syndrome

- AR
- deficiency of **fatty aldehyde dehydrogenase enzyme** due to mutations in the (**FALDH**) gene
- Neuro-cutaneous
  - **Ichthyosis**
  - perifoveal glistening (white dots in the **ocular** fundus)
  - **CNS**: delayed motor development, an abnormal gait, pyramidal signs, spasticity and contractures

(3) Refsum's disease

- AR
- abnormal lipid metabolism
- It is caused by mutations in the **phytanoyl-CoA hydroxylase (PHYH)** = impaired degradation of **phytanic acid**
- Clinical features:
  - **Ichthyosis**
  - **neurologic** symptoms such as weakness, difficulty walking
  - poor night vision / atypical retinitis pigmentosa
  - peripheral polyneuropathy of a mixed motor and sensory type, cerebellar dysfunction and elevated protein levels in the cerebrospinal fluid
  - Other findings can include sensorineural deafness, cataracts, renal tubular dysfunction, cardiomyopathy and skeletal hyperostosis.

(4) Trichothiodystrophy with ichthyosis (IBIDS, PIBIDS)

- **IBIDS**: ichthyosis, brittle hair, infertility, developmental delay, short stature
- **PIBIDS**: ***photosensitivity*** + IBIDS

(5) KID syndrome

- AD
- keratitis–ichthyosis–deafness

(6) CHILD syndrome

- **X-linked dominant**
- Congenital hemidysplasia with ichthyosiform erythroderma (or nevus) and limb defects
    - At birth, unilateral erythema and waxy, yellowish adherent scale; later, verrucous; hyperkeratosis of variable extent
    - Ipsilateral skeletal hemidysplasia
    - organ hypoplasia

Incontinentia Pigmenti (IP)

Definition: A rare **multi-system** genetic disorder

> **NB.** IP may present to neonatologists, neurologists, ophthalmologists or dentists as well as dermatologists. However, the **diagnosis** rests on the **cutaneous** findings.

Synonym: Bloch–Sulzberger syndrome

Pathogenesis:

- **Mode of inheritance:** X-linked dominant
  - Affects females
  - Ante-natally **lethal in boys** مهم جداً

> **IP in boys?**
> 1. Klinefelter syndrome (one or more extra X)
> 2. Mosaicism

- **Genetic defect:** mutations in **NEMO** (NF- κ B essential modulator) gene
  - The NEMO protein (a kinase enzyme) → activates NF-κB (**protects against** TNF-α-induced **apoptosis**)
  - in IP, an apoptotic state occurs → **destruction of epidermal cells**.

Clinical features:

(A) Cutaneous findings:

Four stages (skin lesions ***follow Blaschko's lines***):

1. **Inflammatory/vesicular stage:**
   - **linear** erythema and **blisters** (vesiculo-bullous lesions)
   - during the **first few months** of life
   - an otherwise well مهم جداً baby **girl**
   - most common on the **limbs** and scalp, frequent on the trunk, and rare on the face
   - **resolve** within days to weeks → stage 2
2. **Verrucous stage:**
   - verrucous **linear** plaques
   - favor the **extremities**
   - **disappear** later in infancy

3. **Hyper-pigmented stage:**
   - **Streaks** of reticulate grayish-brown **hyperpigmentation**
   - predilection for the trunk and intertriginous sites, with **scalloped edges** (growth of normal keratinocytes into affected skin)
   - **fade** by **adolescence** (BUT few areas of slate-gray pigmentation may persist lifelong)
4. **Hypo-pigmented/atrophic stage:**
   - From the teen years onward, linear **hypopigmented bands lacking hair and sweat glands**
   - on the posterior aspects of the limbs (especially the calves)
   - may be the only stigmata of the disease during adulthood

NB. Individual stages of IP may be **absent** (developed **intra-uterine**) مهم or overlap
NB. The inflammatory sequence sometimes recurs within pigmented areas during infancy or later in childhood with intercurrent febrile illnesses.

(B) Extra-cutaneous findings: 4 مهمين

Other ectodermal abnormalities (alopecia, nail and teeth affection)

1. **Teeth** (60–80%): missing / pegged / conical
2. **Nails** (10–30%): dystrophic (ridging, pitting > subungual keratoses)

Occasional involvement of the eyes and CNS

3. **CNS** (20–30%): Seizures, Developmental delay, Spastic hemi/di/tetraplegia
4. **Eye** (20 – 40%): Retinal vascular abnormalities / Strabismus / Cataracts / Microphthalmia / Optic atrophy
5. Breast: asymmetric breast development or supernumerary nipples
6. Skeletal (uncommon): Skull anomalies, Scoliosis
7. Pulmonary hypertension (uncommon)

Pathology

1. The early **inflammatory (vesicular)** مهم جداً phase: **eosinophilic spongiosis (DIAGNOSTIC)** + scattered dyskeratotic keratinocytes
2. **Verrucous** lesions: hyperkeratosis, acanthotic epidermis and foci of dyskeratosis
3. **Hyper-pigmented stage**: ***pigmentary incontinence*** + vacuolization of basal keratinocytes
4. **Stage 4:** thinned epidermis and dermis devoid of adnexa

NB. The name IP refers to the pathologic finding of pigmentary incontinence (i.e. dermal melanophages) in the third stage of the disease.

Differential diagnosis

Infectious conditions (e.g. herpes zoster, varicella or herpes simplex viral infections)

- IP → well-being of the child + characteristic pattern of the skin lesions
  - ❋ Peripheral eosinophilia + leukocytosis → common in neonates with IP
  - ❋ Histologic examination → confirmation of the diagnosis

Linear and whorled nevoid hypermelanosis

- ❋ NO preceding inflammatory phase
- ❋ Biopsy shows predominantly epidermal hyperpigmentation rather than dermal melanophages

Hypomelanosis of Ito

- ❋ NO preceding inflammatory phase
- ❋ Adnexa are typically normal

Treatment

- **Ophthalmologic** and **neurologic** evaluations (important – during infancy)
- **Dental** assessment and early intervention when anomalies are present
- The **mother** should be examined and genetic counseling provided

PSEUDOXANTHOMA ELASTICUM (PXE)

Nomenclature:

- Characteristic **cutaneous findings resemble xanthomas** (yellowish papules)
- **Pseudo**-xanthoma ⇨ to differentiate this condition from xanthomas

Epidemiology:

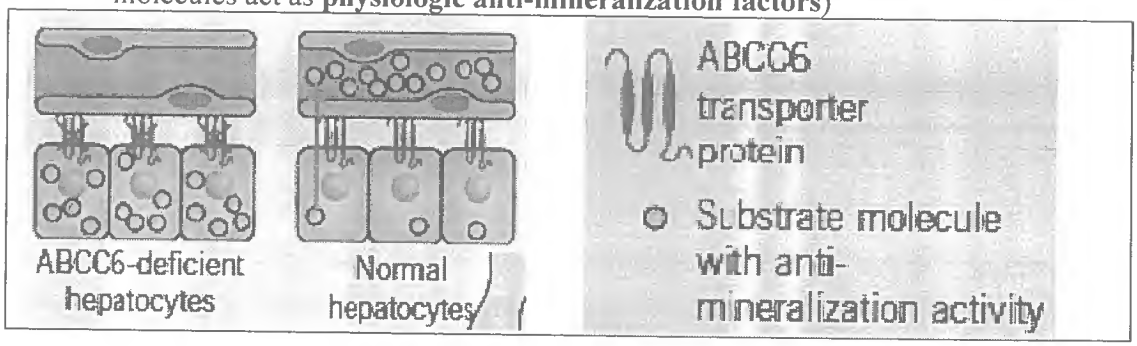
- ***Prevalence:*** 1 in 25 000 – 1 in 100 000
- ***Race:*** **ALL** races without geographic predilection
- ***Sex:*** a slight **female** preponderance
- ***Age:*** **Skin** changes → usually appear during **childhood**
  - BUT the **diagnosis** is frequently **not made until** serious systemic or ocular complications develop in the **3rd or 4th decade** of life.

Pathogenesis:

- ***Mode of inheritance:*** **AR**
  - ☆ **Mild** cutaneous & ocular findings have been observed in **heterozygous carriers**
- ***Genetic defect:*** Loss-of-function **mutations** in both copies of the ATP-binding cassette sub-family C member 6 gene (**ABCC6**)

Inhibition of ectopic mineralization

- The normal **liver** expresses high levels of the ABCC6 protein
- **ABCC6** acts as an **efflux pump** on the basolateral surface of hepatocytes, **transporting molecules** from inside these cells **to the circulation** (these molecules act as **physiologic anti-mineralization factors**)



In PXE, **absence of ABCC6** → ↓ circulating concentrations of these molecules (physiologic anti-mineralization factors) → decreased plasma anti-mineralization capacity → progressive **mineralization (calcium deposition) of elastic fibers** in target organs **(3)**

1. mid and deep dermis (**skin**)
2. media and intima of mid-sized arteries (**CVS**)
3. Bruch's membrane of the **eye**

Clinical Features:

PXE primarily affects the **elastic fiber** networks of the **skin**, **eyes** and **cardiovascular** system (3)

- great ***variability*** in ***severity***
- sometimes, ***only one or two*** of these organ systems are affected

(1) Cutaneous findings:

- The ***most frequent*** manifestation of the condition
- ***Characteristic***
- ***Thin, yellowish papules*** (resemble xanthomas) appear during the 1st or 2nd decade of life ⇨ coalesce ⇨ ***cobblestone-like*** plaques ⇨ a "***plucked chicken skin" appearance***
- Typically appear in **flexural** areas. The **lateral neck** is usually affected **first**. **Other flexural sites** that may be affected include the antecubital and popliteal fossae, wrists, axillae, groin and periumbilical area in multiparous women
- Involvement of **non-flexural sites** = more **extensive** disease.
- With advanced disease ⇨**firm papules or plaques** (due to increased dermal **calcium deposition**) ⇨extrusion of this yellowish material through the epidermis **"perforating PXE"** مهم جداً

Impaired function of the elastic fiber network → loss of recoil → **sagging** of the skin (most notable in the **axillae and groin**)

Mucosal involvement (yellow papules) → most often on the **lower lip**

(2) Ocular findings:

- **Angioid streaks** مهم جداً
  - ☆ may be evident as early as the 1st decade of life
  - ☆ can be found in virtually all PXE patients by 30 years of age
  - ☆ usually **asymptomatic**
  - ☆ **breaks (cracks, fractures)** in the **calcified elastic lamina** of **Bruch's membrane** (derived from the retina and choroid plexus) → may lead to choroidal **neovascularization** → the newly formed vessels are prone to **hemorrhage** with subsequent **scarring** (this process ultimately results in progressive **loss of vision**, especially in central fields – usually becomes apparent after 40 years of age and leads to legal blindness)

☆ **Angioid streaks** are highly **characteristic** but **not pathognomonic** of PXE = ***Other causes of angioid streaks:*** مهم جداً

- Paget's disease of the bone
- EDS
- Sickle cell anemia
- Thalassemia
- Lead poisoning
- Age-related degeneration of Bruch's membrane

- **Mottling of the retinal pigment epithelium** (peau d'orange changes)
  ☆ Actually the **most prevalent** ophthalmologic finding in PXE
  ☆ May **precede** the development of angioid streaks

- **Other less common features:** e.g. macular degeneration, optic drusen and "owl's eyes" (paired hyperpigmented spots)

(3) Cardiovascular manifestations:

- often cause significant **morbidity** and may even result in **early death**
- PXE affects primarily **mid-sized arteries**, especially of the **extremities**
- Progressive **calcification** of the **elastic media and intima** leads to the formation of **atheromatous plaques**.
- **Sequelae:** (occur at a much ***younger age*** than in the general population)
  1. **Extremities:** Claudication, loss of peripheral pulses
  2. **Heart:** angina pectoris, myocardial infarction
  3. **GIT:** Calcified blood vessels of the gastric and intestinal mucosa → increased liability for hemorrhage (gastrointestinal **bleeding**) particularly from the **stomach**
  4. **Others:** renovascular hypertension, stroke
- **NB.** Patients with PXE also have an increased prevalence of **mitral valve prolapse**.

Pathology:

Characteristic light microscopic changes in the **skin**: (Similar changes are observed in the **media** of **mid-sized arteries**)

- distorted, **fragmented elastic fibers** in the mid and deep reticular **dermis**
- In advanced cases → **calcium deposits** on these altered elastic fibers
  ☆ routinely stained sections → visible in as **purple** clumps
  ☆ stains for elastin (e.g. **Verhoeff–van Gieson**) and calcium (**von Kossa**) are sometimes necessary to visualize the characteristic alterations in the elastic fibers.

NB. In some patients **without skin manifestations** who are suspected to have PXE because of other findings, such as angioid streaks, a diagnosis may be confirmed by **biopsy** of a **pre-existing scar**.

NB. Serum levels of calcium and phosphate are normal مهم جداً

Differential Diagnosis:

(1) Photoaging: actinic damage within chronically sun-exposed sites:
- ☆ can clinically mimic the yellowish, lax plaques of PXE
- ☆ BUT
  - o in older individuals (PXE first manifest in younger patients)
  - o involves the neck but not the axillae or groin

(2) Other fibroelastolytic skin disorders e.g. مهم جداً
- ☆ PXE-like papillary dermal elastolysis
- ☆ White fibrous papulosis of the neck

BOTH .. NO systemic affection

(3) Acquired PXE مهم جداً

Skin lesions with the **same morphology and distribution** as PXE and similar histologic features have been observed

1. in patients receiving **D-penicillamine** (interferes with desmosine cross-linking in elastin)
2. after local exposure to **saltpeter**
3. in longstanding end-stage **renal** disease
4. in L-tryptophan-induced eosinophilia myalgia syndrome (historically)

- ☑ **Ophthalmologic** and **cardiovascular** findings are **absent**
- ☑ **Skin** lesions may **resolve** after cessation of the causative exposure or (in patients with renal disease) normalization of the serum calcium– phosphate product.
  - o **penicillamine**-induced PXE-like skin changes → **von Kossa stain** is **negative** (**no calcification** of the abnormal fibers)
  - o **saltpeter** exposure and end-stage **renal** disease → calcification occurs and this stain is positive.

Treatment

Multi-disciplinary approach management of PXE

SKIN

- No specific treatment is available
- Surgical intervention for excessive skin folds

EYES

Prevention and early detection

- ☆ Biannual funduscopic examination
- ☆ Regular assessment for central visual field defects
- ☆ Use of sunglasses
- ☆ Diet/vitamins rich in antioxidants
- ☆ Avoidance of head trauma, heavy straining and smoking

Treatment

- ☆ Laser photocoagulation for choroidal neovascularization

CARDIOVASCULAR SYSTEM

Prevention and early detection

- ☆ Baseline ECG and echocardiogram
- ☆ Annual cardiac examination
- ☆ Healthy lifestyle with balanced diet, regular exercise, weight control, and avoidance of smoking and excessive alcohol intake
- ☆ **Magnesium** supplementation (A diet high in magnesium was shown to reduce connective tissue mineralization in a mouse model of PXE)
- ☆ Moderate calcium intake (as appropriate for age)
- ☆ Low-dose therapy with acetylsalicylic acid if not contraindicated

Treatment

- ☆ Correction of hyperlipidemia and hypertension
- ☆ Low-dose acetylsalicylic acid, pentoxyfylline, cilostazol or clopidogrel for intermittent claudication

Inherited Disorders Characterized by Defective DNA Repair

The major disorders characterized by **both defective DNA repair** and **photosensitivity** are:

1. Xeroderma pigmentosum (**XDP**)
2. **Cockayne** syndrome
3. **UV-sensitive syndrome**
4. the photosensitive form of **trichothiodystrophy**

ALL are caused by defects in one of the **nucleotide excision repair (NER)** proteins

Nucleotide excision repair (NER)

UV-induced DNA damage

- Different wavelengths of **UV light** induce different types of **DNA damage**.
- UV light is capable of exciting the DNA molecule directly and subsequently generates DNA **photoproducts**
- DNA photoproducts are **dimers**, formed by ***covalently binding two adjacent pyrimidines in the same polynucleotide chain*** i.e. **pyrimidine dimers** (cyclobutane dimers and 6,4-photoproducts).

Enzymes (proteins) of the NER

1. **Helicase** = Unwinds the DNA helix around the DNA lesion
2. **Endonuclease** = cuts at the single-strand around the DNA lesion
3. **Polymerase** = attaches new complementary nucleptides
4. **Ligase** = closes the nick between the newly synthesized DNA and the parental strand

Xeroderma pigmentosum (XP)

XDP is condition associated with a marked increase in the development of **malignancies** بشكل عام, especially cutaneous.

Epidemiology / Incidence:

- 1 per million in newborns in Western countries
- 1 per 100 000 newborns in Japan

Pathogenesis

☆ ***Mode of inheritance:*** AR

☆ ***Defect:***

In XP, there are 7 genetically different **complementation groups (A → G)**, each associated with a **different site of impairment (protein)** in nucleotide excision repair (**NER**) pathway

⇨ impairment in the removal of DNA damage from any part of the genome ⇨ damaged DNA accumulates ⇨ mutations and cancer

XP variant ⇨ has **normal NER**. It is due to mutations in the gene that encodes **DNA polymerase-η (eta)** ﻫ (**Pol η** or **Pol H**) ⇨ responsible for **bypassing the unrepaired DNA photoproduct during DNA replication**

- Mutations ⇨ insertion of erroneous residues during replication.

Phototesting in XP patients has shown the **action spectrum** for **inflammatory erythema** of the skin to be in the **290 to 340 nm (UVB, UVA)** ﻫ range. The **MEDs** corresponding to those wavelengths are generally quite **reduced**, with the peak responses often vesicular and delayed by a day or two.

Clinical features:

3 (skin, eye, neuro) – what is this association????? + **internal malignancies**

(I) SKIN

1. Marked **photosensitivity**
2. Early onset of all major types of **skin cancer**

STAGES according to age

1. Starting from an early age → easily develop ***sunburns*** with erythema, edema and vesicles following minimal sun exposure
2. By the age of 2 years → practically all patients have developed ***solar lentigines***
3. With continuing exposure → the skin gradually becomes ***xerotic***, leading to the term 'xeroderma pigmentosum', or dry pigmented skin
4. Then → ***malignant tumors*** = actinic keratoses, basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs) and, less frequently, melanomas develop prematurely in sun-exposed sites
   ☆ NB. the median age for initial non-melanoma skin cancer development was 8 years

(II) Ocular abnormalities (40% of patients)
Severe photophobia, keratitis, corneal opacification and vascularization
Loss of eyelashes, ectropion, and SCC and melanoma of the UVR-exposed parts of the eyes

(III) Neurologic abnormalities (20–30% of XP patients)
(due to defective DNA repair in nerve cells, resulting in neuronal death)

- Some XP patients develop a **limited number of clinical manifestations**, such as isolated hyporeflexia and progressive deafness

- **DeSanctis–Cacchione syndrome**
  - ☆ the ***most severe*** presentation
  - ☆ microcephaly, progressive mental retardation, retarded growth and sexual development, deafness, choreoathetosis, ataxia and quadriparesis

- **XP variant** patients usually have مهم **NO neurologic problems**

(IV) Internal malignancies:

- Patients with XP have 10- to 20-fold increase in the incidence of **internal malignancies**, including tumors of the brain, lung, oral cavity, gastrointestinal tract, kidney and hematopoietic system.

Treatment:

1. Extremely rigorous **photoprotection** أول هام
   - Oral **calcium** and **vitamin D** supplementation
2. **Screening** tests for the presence of **neurologic** involvement:
   - Deep tendon reflex testing
   - Routine audiometry
3. **Management of the premalignant and malignant skin tumors**:
   - Cryotherapy, electrodesiccation and curettage, topical imiquimod and surgical excision
   - **Oral retinoids** can be administered as **chemopreventive** agents
4. **Topical** application of the **bacterial DNA repair enzyme** T4 endonuclease V (**T4N5**) formulated in a liposomal delivery vehicle has been successful in decreasing the development of actinic keratoses and BCCs (this product is currently ***not commercially available***)

Cockayne syndrome (CS)

Defective NER
Two complementation groups: **CS-A** and **CS-B** with **identical** phenotypes

Photosensitivity ***without pigmentary*** changes
No increase in ***malignancies*** in "pure" CS

- Loss of adipose tissue, prominent ears, dental caries, thinning of skin and hair
- Hypogonadism, stooped posture, joint contractures, short stature with extremely thin body habitus ("cachectic dwarfism"), microcephaly, mental retardation, deafness
- Calcification of basal ganglia, demyelination, pigmentary retinal degeneration, osteoporosis

1) **CS type I:** 80% of patients; onset at 2 years of age, progressive; life expectancy: second to third decades
2) **CS type II:** symptoms at birth, life span = 6–7 years
3) **CS type III:** late onset, normal growth and development

Combined XP/CS: solar lentigines, skin ***cancers***, ***pigmentary*** retinal degeneration, basal ganglion calcification

Tuberous sclerosis (TS) & Neurofibromatosis (NF)

BOTH

- **Neuro-cutaneous** disorders (**phakomatoses**) = cutaneous + EYE + peripheral and/or central nervous system neoplasms.
- Hereditary cancer syndromes = **mutations** in ***tumor suppressor genes***
- Autosomal dominant (**AD**) inheritance
    - new cases (about **50%**) represent ***de novo*** **mutations.**

Tuberous sclerosis (TS)	Neurofibromatosis (NF)
Synonyms: Tuberous sclerosis complex (TSC) **Epiloia** (**epi**lepsy, **lo**w **i**ntelligence, **a**ngiofibroma) Bourneville disease	**Synonyms:** NF-1 = von Recklinghausen disease
Pathogenesis: ***Mode of inheritance:*** AD ***Defect:*** mutations in 2 genes: • **TSC1** gene on chromosome **9** = encoding **hamartin** • **TSC2** gene on chromosome **16** = encoding **tuberin** ***Both hamartin and tuberin are tumor suppressor genes***	**Pathogenesis:** ***Mode of inheritance:*** AD ***Defect:*** mutations in NF-1 gene = encodes **neurofibromin** (***tumor suppressor gene***)
Incidence: **Rare** (1 in 10 000 births)	**Incidence:** (1 in 3 000 births)
Clinical picture:	**Clinical picture:**
Cutaneous: 5 مهم جدا جدا جدا 1. ***Facial angiofibromas (Adenoma sebaceum):*** pink to red or red–brown **papules** or papulo-nodules, which may coalesce into plaques. The papules are often dome-shaped and have a smooth, shiny surface and have a **bilateral** and **symmetric** distribution classically affecting **naso-labial folds** مهم جدا.	**Cutaneous:** 1. **Neurofibromas:** soft sessile dome-shaped nodules that may become pedunculated • **Plexiform neurofibrom** = along course of nerve 2. **Café-au-lait macules (CALMs):** the earliest sign: tan to dark brown spots 3. **axillary freckling (Crowe's sign)** مهم جدا

2. ***Peri- & Sub-ungual fibromas:*** periungual papules or nodules (**Koenen tumors** مهم جدا) 3. ***Hypomelanotic (Ash leaf) macules:*** usually present **at birth** or within the first few months of life (**earliest sign of TS** مهم جدا). They are not depigmented (as in vitiligo) but are hypopigmented. Wood's light can help to diagnose these lesions. 4. ***Guttate leukoderma:*** multiple 1-2 mm hypopigmented "**confetti**" macules. 5. ***Shagreen patch:*** connective tissue nevus (**collagenoma**). Occur most commonly in the **lumbosacral** area	
Ocular: Retinal **hamartomas / gliomas** (NO vision affection = peripherally located)	**Lisch nodules = melanocytic hamartomas , bilateral on iris** مهم Optic glioma +Others
Neuro: **Seizures / epilepsy** مهم **Mental retardation** مهم CNS calcification and tumors (astrocytoma) **Cortical tubers** (an abnormal growth of neuronal and glial cells (can be detected by neuroimaging e.g. MRI)	Neuro CNS tumors
Heart: rhabdomyoma (cause of death) **Renal:** Multiple bilateral angiomyolipomas **Other systems:**	**Adrenal** **Pheochromocytoma = HTN (cause of death)**
Histopathology: ***Hypopigmented macules:*** ↓↓ amount of epidermal melanin but a normal number of melanocytes	**Histopathology:** CALM: ↑ amount of melanin NF: dermal collection of nerve fibers (thin, spindle-shaped and wavy)

Angiofibromas: proliferation of fibrous tissue and blood vessels. Sebaceous glands are normal in size and number ***The shagreen patch + periungual fibromas = collagenomas*** (the dermis is replaced by thick bundles of collagen, and elastin fibers are typically absent).	
Treatment: 1. ***Genetic counseling*** to affected individuals and families. 2. ***Investigations*** for systemic affection & complications 3. ***Management of facial angiofibromas (cosmetic):*** dermabrasion, electrosurgery and treatment with ablative (CO_2) and pulsed dye (for thinner erythematous lesions) lasers **NB. the lesions often <u>recur</u> after treatment.** 4. **Targeted therapy with the mTOR inhibitor rapamycin** مهم • **Oral**: ↓ size of renal angiomyolipomas / improvement of lung function / regression of TS-associated subependymal giant cell astrocytomas / improvement of facial angiofibromas (ALSO with topical administration of rapamycin 1% solution or ointment)	1 2 3 management of NF Surgical excision + ...

DIAGNOSTIC CRITERIA FOR NF-1

Two or more of the following must be present:

1. Six or more café-au-lait macules >5 mm in prepubertal individuals and >15 mm in postpubertal individuals
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. "Freckling" in the axillary or inguinal regions
4. Optic gliomas
5. Two or more Lisch nodules (iris hamartomas)
6. Osseous lesion, such as sphenoid wing dysplasia or thinning of long bone cortex, with or without pseudarthrosis
7. First-degree relative (parent, sibling or offspring) with NF1 by the above criteria

DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS COMPLEX

	MAJOR FEATURES	MINOR FEATURES
Cutaneous	Facial angiofibromas Ungual or periungual fibromas ≥ 3 Hypomelanotic macules Shagreen patch	"Confetti" hypopigmented skin lesions
Extra-cutaneous	Multiple retinal nodular hamartomas Renal angiomyolipoma Cortical tubers Subependymal nodules Subependymal giant cell astrocytoma Cardiac rhabdomyoma, single or multiple Lymphangioleiomyomatosis	Multiple, randomly distributed pits in dental enamel Gingival fibromas Retinal achromic patch Cerebral white matter radial migration lines Multiple renal cysts Hamartomatous rectal polyps Bone cysts Non-renal hamartoma
Definite TS: two major OR one major feature + two minor features Probable TS: One major + one minor feature Possible TS: Either one major feature or two or more minor features		

OTHER Genodermatoses